Science of the Total Environment 773 (2021) 145525

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Why airborne transmission hasn't been conclusive in case of COVID-19? An atmospheric science perspective

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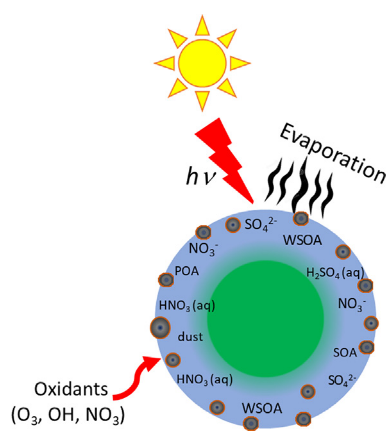
HIGHLIGHTS

- An atmospheric science perspective on airborne transmission is reported
- Co-morbidity of SARS-CoV-2 vs air pollution is presented
- Measurement of their infectivity and viability is highly uncertain due to lack of robust sampling system to separately
- This may help us better understand the airborne transmission of COVID-19

GRAPHICAL ABSTRACT

Schematic diagram showing interaction of droplet nuclei with particulate matter, radiation and oxidants in the atmosphere. POA and WSOA are primary organic aerosol and water-soluble organic aerosols components of the particulate matter.



Abbreviations: CoV, Coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus; MERS, Middle East respiratory syndrome; COVID-19, Coronavirus disease-2019; Droplet nuclei, Smaller droplets (≤5 μm) laden with CoV-2; Droplets, CoV-2 laden droplets (>5 μm) produced during talking, coughing or sneezing; PM, Particulate matter; $t_{1/2}$, Half-life of COVID-19 virus; T, Ambient temperature; RH, Relative humidity (%).

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https://doi.org/10.1016/j.scitotenv.2021.145525

A R T I C L E I N F O

Article history:
Received 16 December 2020
Received in revised form 15 January 2021
Accepted 26 January 2021
Available online 1 February 2021

Editor: Philip K. Hopke

Keywords:
COVID-19
Air pollution
Mortality
Droplets
SARS CoV-2

A B S T R A C T

Airborne transmission is one of the routes for the spread of COVID-19 which is caused by inhalation of smaller droplets[1] containing SARS-CoV-2 (i.e., either virus-laden particulate matter: PM and/or droplet nuclei) in an indoor environment. Notably, a significant fraction of the small droplets, along with respiratory droplets, is produced by both symptomatic and asymptomatic individuals during expiratory events such as breathing, sneezing, coughing and speaking. When these small droplets are exposed to the ambient environment, they may interact with PM and may remain suspended in the atmosphere even for several hours. Therefore, it is important to know the fate of these droplets and processes (e.g., physical and chemical) in the atmosphere to better understand airborne transmission. Therefore, we reviewed existing literature focussed on the transmission of SARS-CoV-2 in the spread of COVID-19 and present an environmental perspective on why airborne transmission hasn't been very conclusive so far. In addition, we discuss various environmental factors (e.g., temperature, humidity, etc.) and sampling difficulties, which affect the conclusions of the studies focussed on airborne transmission. One of the reasons for reduced emphasis on airborne transmission could be that the smaller droplets have less number of viruses as compared to larger droplets. Further, smaller droplets can evaporate faster, exposing SARS-CoV-2 within the small droplets to the environment, whose viability may further reduce. For example, these small droplets containing SARS-CoV-2 might also physically combine with or attach to pre-existing PM so that their behaviour and fate may be governed by PM composition. Thus, the measurement of their infectivity and viability is highly uncertain due to a lack of robust sampling system to separately collect virions in the atmosphere. We believe that the present review will help to minimize the gap in our understanding of the current pandemic and develop a robust epidemiological method for mortality assessment.

Contents

1. Introduction

The coronavirus disease (COVID-19) has still not fully subsided and even, second and third waves have been reported in different parts of the world. The COVID-19 pandemic so far has infected more than 106 million people and has killed more than 2.3 million people across the world.[2] This is the third zoonotic outbreak in the last two decades which is caused by the coronavirus family. For instance, the two coronavirus outbreaks were caused by SARS-CoV in 2002–2003 and SARS -CoV-2 in late 2019 whereas the other one, Middle East respiratory syndrome (MERS)-CoV in 2012. The first two disease outbreaks have been traced back to China and the other to Middle East countries. The SARS-CoV-2 is coronavirus that causes COVID-19 disease. Notably, all the three diseases cause severe acute respiratory syndrome (SARS), however, their infectivity rate and mortality vary significantly (Table 1).

The epidemic of SARS-CoV-1 caused 8422 illnesses and 916 deaths in 29 countries (WHO, 2020; CDC, 2017) whereas MERS-CoV caused an epidemic claiming the lives of 866 people in 27 countries (WHO, 2020). It is found that about 90% of amino acid sequence in nucleocapsid (N) protein of SARS-CoV-2 was identical with SARS-CoV (Kannan et al., 2020; Zhou et al., 2020). The scanning electron microscopic (SEM) analysis has confirmed the presence of spikes that makes the CoV-2 pathogen more infectious (Mallapaty, 2020). Like all other proteins, the spikes are made of specific combinations of amino acids, which tend to curl up into a helix or stretch out into a sheet.

Table 1
A comparison of reproductive number (R_0) of some human infectious agents (adopted from Tang et al. (2006) and references therein). R_0 for SARS-CoV-2 is taken from Petersen et al. (2020).

Virus	R_0 number
SARS-CoV2	2–2.5
SARS-CoV	2–3
Flu virus	1.3
Measles virus	15–17
Bordetella pertussis	15–17
Chickenpox virus	10–12
Rubella virus	7–8
Smallpox virus	4–7
Influenza virus	1.7–20
MERS-CoV	3–6.6

[1]Droplets have diameter >5 μm (also called as respiratory droplet) whereas those with diameter ≤5 μm are termed as smaller droplets (also known as aerosols, nano-droplet or droplet nuclei).
[2]https://www.worldometers.info/coronavirus/, accessed on 12 January 2021.

Although droplet transmission either via droplet inhalation or physical contacts is considered as the major route of transmission in COVID-19, airborne transmission has remained controversial since the beginning and several researchers have been appealing to the medical community as well as relevant national/international bodies to recognize airborne transmission as another probable route for the spread of COVID-19 (Drahl, 2020; Morawska and Milton, 2020; Zhang et al., 2020). Moreover, though the Centers for Disease Control and Prevention (CDC) updated the guidelines for potentiality of airborne transmission of COVID-19,[3] the World Health Organization (WHO) have been very cautious at the beginning of declaring the airborne transmission as another route of transmission for the spread of COVID-19. The WHO was initially insisting only on avoiding close contacts and following strict hand sanitization to prevent the spread of COVID-19 through droplet transmission. However, the WHO has now accepted the possibility of airborne/aerosol transmission but this acceptance is partial as it is tagged with the phrase “in specific circumstances and settings in which procedures that generate aerosols are performed”.[4]

Recently, a team of 239 scientists wrote an open letter to WHO citing evidences for potential airborne transmission of SARS-CoV-2. Since then, there are numerous studies wherein several researchers have not only tried to measure SARS-CoV-2 in poorly ventilated indoor environments (Asadi et al., 2019; Chia et al., 2020; Li et al., 2020; Qian et al., 2020) but also on different outlets as well as on surfaces. In addition, current research is not only focussed on the measurement of SARS-CoV-2 in ambient air and in particulate matter but also on the isolation of SARS-CoV-2 from these matrices followed by culture experiments. This would help to better understand their viability and behaviour. Besides, several researchers are now invoking to minimize airborne transmission of COVID-19 in indoor environments (Hogeling et al., 2020). Thus, the mounting evidences (Hoseinzadeh et al., 2020; Lewis, 2020; Wathore et al., 2020) and more recent studies in support of airborne transmission point toward another route of transmission of SARS-CoV-2 for COVID-19 spread (The Lancet Respiratory), especially in indoor environments, e.g., poorly ventilated air-conditioned restaurants (Asadi et al., 2020; Chia et al., 2020; Eissenberg et al., 2020; Fears et al., 2020; Hsiao et al., 2020; Li et al., 2020; Liu et al., 2020; Lu et al., 2020; Miller et al., 2020; Morawska and Cao, 2020; Morawska and Milton, 2020; Qian et al., 2020; Santarpia et al., 2020; Setti et al., 2020a; Setti et al., 2020b; van Doremalen et al., 2020; Ye et al., 2020; Zhang et al., 2020). Nonetheless, there has been an inconclusive scientific opinion about airborne transmission with very limited understanding mainly because of challenges associated with sampling smaller droplets containing SARS-CoV-2 for analysing their viability and infectivity in the environment. This lack of scientific data has also led to a poor understanding of physical/chemical processes and the fate of the small droplets in the indoor environment and the ambient atmosphere. Here, we evaluate the findings of the various studies focused on the mode of transmission of SARS-CoV-2 and identifying the associated gaps in the studies that thwart the research community to be conclusive on the air-borne transmission of SARS-CoV-2. Moreover, our study also provides suggestions to bridge these gaps to improve the research on the airborne transmission of SARS-CoV-2.

2. Airborne transmission: definitions and evidences

2.1. Definition of droplets vs aerosols

One of the reasons for discrepancy and disagreement is the erroneous nomenclature of the droplets leading to an improper definition of airborne/aerosol transmissions. A continuum of droplets of different sizes containing SARS-CoV-2, ranging from a minimum of ~0.6 μm to 1000 μm (or even larger size), are produced during an expiratory event such as breathing, sneezing, coughing and speaking (Aliabadi et al., 2011; Gralton et al., 2011; Mittal et al., 2020; Vejerano and Marr, 2018). Therefore, droplets of all the sizes containing SARS-CoV-2 in the atmosphere can be collectively called as an aerosol[5] and this is probably why droplet and aerosols are sometime interchangeably used in the medical science. Thus, in strict sense, droplet transmission is not a realistic route for a viral infection by the respiratory route. Thus, a part of droplet transmission which focuses only on small droplets while they are floating in the air, is included in the aerosol transmission (Fig. 1). Moreover, the definition of an aerosol or droplet in medical science is not confined to wet materials only. For example, the remnants of smaller droplet are commonly referred as “droplet nuclei” which results from the drying of its moisture content, although no one knows whether the droplet nuclei have water or not, or if it has, what amount of water it has.

Secondly, one cannot inhale large droplets and if we consider gravitational force acting on them, bigger droplets cannot stay in the atmosphere for a longer time and will settle down at a surface in close proximity (Fig. 1). In contrast, smaller droplets will still keep floating in the atmosphere for a longer time. Thus, if we assume droplets as continuum of different sizes containing SARS-CoV-2, bigger droplets no longer can be called as an aerosol and it becomes just a subset of entire droplet continuum. Nevertheless, both these droplets can cause transmission of SARS-CoV-2 but their mode of transmissions will be different. The question arises as how to differentiate various modes of transmission in a viral disease spread. Therefore, the concept of “cut-off sizes” for small and large droplets was developed originally by Wells in the 1930s (Wells, 1934) and the same definition has been continued since then. As per Well's definition and subsequently also adopted by WHO,[6] droplets with diameter >5 μm (also called as respiratory droplet) are primarily responsible for droplet transmission in COVID-9 and spread of other viral diseases. In contrast, droplets with diameter ≤5 μm are termed as smaller droplets (also known as aerosols, nanodroplet or droplet nuclei) and are mainly associated with airborne/aerosol transmission (Fig. 1). The droplet nuclei generally result either from evaporation of a bigger droplet containing SARS-CoV-2 or surface attachment of virus with PM (i.e. PM laden with virus). However, it should be noted that there is no “cut-off size” between droplet nuclei and smaller droplet that are afloat in the air but both have size ≤5 μm (Fig. 1).

2.2. Absence of a strict definition of the droplet and aerosol transmission

As discussed above, direct/droplet transmission via bigger droplets is the dominant route of transmission in many infectious diseases, which occurs via droplets of size >5 μm. While the terminology and scientific understanding for droplet transmission are quite good, there are still confusions regarding the terminology being used for airborne / aerosol transmission. ‘Airborne transmission’ is synonymously and interchangeably referred as ‘aerosol transmission’ in the literature. The airborne transmission and aerosol transmission are the same phenomenon, except that the former is focusing on the air that conveys the aerosol and the latter is focusing on the particles that convey the pathogen. It is clear from the above discussion that these airborne/aerosol transmissions are caused either by droplets of sizes ≤5 μm or a smaller droplet containing SARS-CoV-2 interacts with an atmospheric aerosol, making it a pathogen-laden particle in air (i.e., infectious atmospheric aerosol or PM), which may subsequently be deposited onto a surface or inhaled

[3] https://www.cdc.gov/media/releases/2020/s1005-how-spread-covd.html.

[4] WHO reference number: WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.2, https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.

[5] Any material (solid particles or liquid droplet) that float in the atmosphere is defined as aerosols. In atmospheric science, we call them aerosol, ambient aerosol, atmospheric aerosols or particulate matter (PM). PM almost have the same size distribution range as droplets containing CoV-2. Thus, ambient aerosol and aerosol/droplet are used in atmospheric science and medical science, respectively. However, aerosol/airborne transmission is exclusively used in medical science only.

[6] WHO reference number: WHO/2019-nCoV/Sci_Brief/Transmission_modes/2020.2.

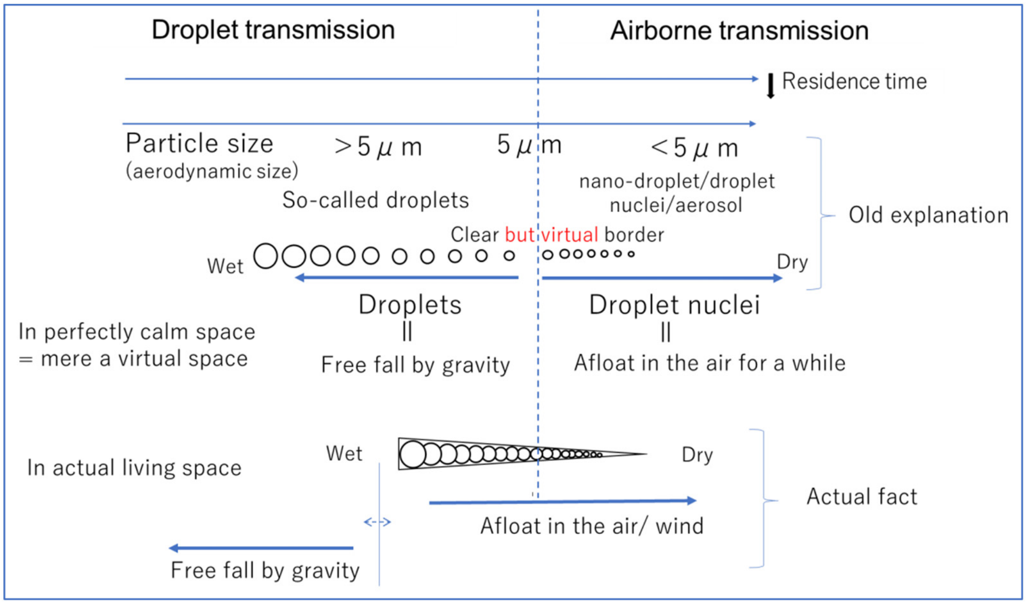

Fig. 1. The conceptual illustration of the definition of droplets, droplet nuclei and nano-droplet. This border depends on the strength of airflow in the space. Note that the size of droplet is used only for illustrative purpose and is not to scale.

by a susceptible person. Thus, unlike droplet transmission which occurs via direct or indirect physical contact with larger droplets by recipients' mouth, nose or conjunctiva (Fig. 2), airborne transmission is either caused by inhalation of droplet nuclei or smaller droplets containing SARS-CoV-2 attached to PM. A classification of different modes of transmission of SARS-CoV-2 is shown in Fig. 2.

A clear definition or terminology is needed to strictly distinguish the two modes of transmissions as it will form the basis to define the specific method of prevention for COVID-19. According to Jones and Brosseau (2015), aerosol transmission reflects a modern understanding of aerosol science and allows physically appropriate explanation and intervention selection for infectious diseases. Therefore, to avoid confusion, in this paper, we will refer 'droplet' as directly ejected aerosols during talking, coughing or sneezing containing SARS-CoV-2 with diameter >5 μm whereas 'aerosol or nano-droplet or droplet nuclei' with diameter ≤5 μm. Further, we would use the term 'particulate matter/atmospheric aerosols/ambient aerosols' which provides a surface for interaction/attachment with droplets containing SARS-CoV-2.

2.3. Evidences in support of airborne transmission

Airborne transmission of infectious diseases has been proposed in earlier studies (Lei et al., 2018; Morawska, 2006; Morawska et al., 2017; Tang et al., 2006; Wei and Li, 2016). For example, Tang et al.

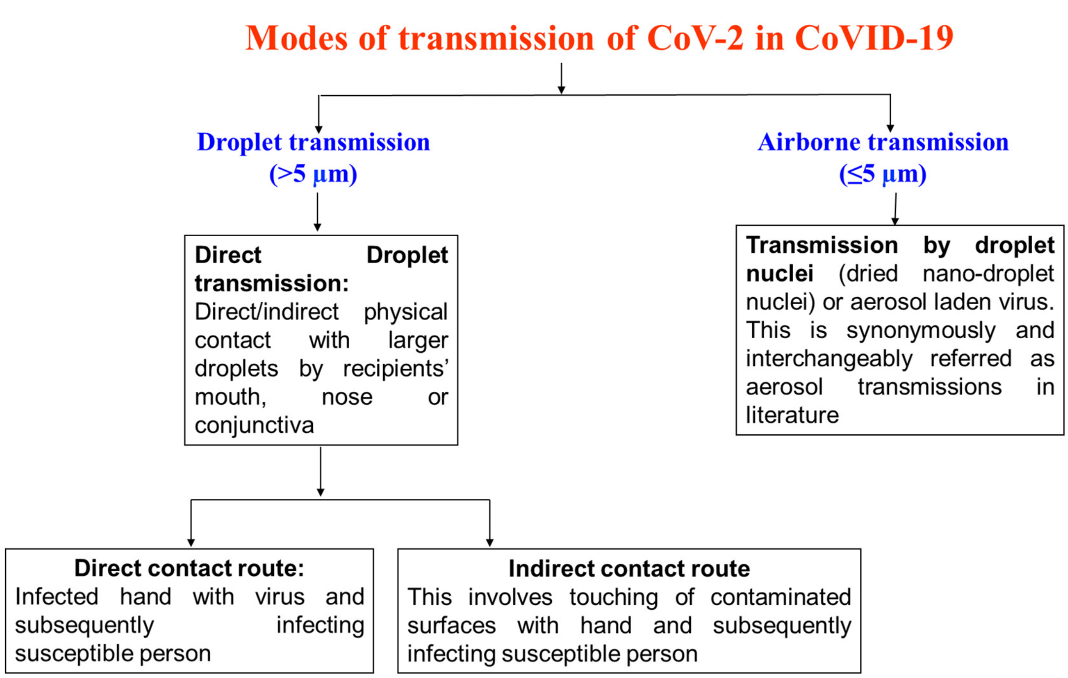

Fig. 2. Classification of different modes of transmission of SARS-CoV-2 in COVID-19. The cut-off diameter of 5 μm is used to distinguish between airborne and droplet transmission.

(2006) studied various factors involved in the aerosol transmission for infection and its control in healthcare premises. It is important to note that SARS-CoV-2 can be transmitted not only by coming in direct contact with the infected droplets, but also by inhaling droplet nuclei and/or by virus attached to a susceptible host particle (Fig. 2). The host particle can be pre-existing PM in the air (Belosi et al., 2021; Nor et al., 2021). As discussed above, aerosols produced during an expiratory event have a size range of ~0.6 μm to 1000 μm. Larger droplets will fall close to the source in a very short time due to gravity. However, smaller/nano droplets are likely to be lingering in the atmosphere for a longer time until they are inhaled or until they collide with another smaller droplet and become sufficiently larger to subsequently settle down under gravity or get attached to a pre-existing atmospheric aerosol (Belosi et al., 2021).

Previous studies suggest the dominance of submicron particles (0.3–1 μm) in a neonatal intensive care unit and centralized hospitals with heating, ventilation and air conditioning (HVAC) systems (Licina et al., 2016). High concentrations of indoor PM are mostly of submicron sizes and their concentrations are strongly associated with human occupancy, which can be even higher if there is an absence of proper ventilation in the indoor environment and thus, smaller droplets may get attached to a pre-existing particulate matter. Environmental contamination of SARS-CoV-2 in air exhaust outlets in Singapore (Ong et al., 2020) and Sweden (Nissen et al., 2020) has been reported recently wherein swab sample collected from these outlets were tested positive, suggesting that smaller virus-laden aerosols might have been displaced by airflows and deposited on vents. The presence of SARS-CoV-2 in vents indicates the possible route of airborne transmission but it's very difficult to establish a connection and to distinguish the two modes of transmissions (droplet vs airborne) as the size-distributions were not measured in these studies. Although the infection probability via airborne transmission may be lower than the droplet transmission, the former has a longer residence time in the atmosphere and thus, is more prone to cause secondary infections, especially in indoor environments. In an earlier study, it has been suggested that coronaviruses have high mutation and gene recombination rates which make them ideal for pathogen evolution (Su et al., 2016). Nonetheless, it is even more important to know the fate, deposition, degradation and infectivity of these smaller droplets in indoor environments to control the spread of COVID-19.

3. Infectivity of smaller vs larger droplets

Like the spread of virus in most of the viral diseases, the infectivity and mode of transmission strongly depends on the physico-chemical characteristics of droplet and subsequently on the binding protein of the virus (Vejerano and Marr, 2018). Therefore, the number density and the size-distribution of droplets produced by an expiratory event largely decide the infectivity whereas the ejection velocity (and size-distributions) determines the mode of transmission of the virus (Mittal et al., 2020). It is estimated that a single sneeze event can generate ≥10^4 droplets, a coughing event generates ~10^2–10^3 droplets whereas talking generates only ~50 particles per second. The studies of size-distribution of droplets in an expiratory event, using an optical particle counter (OPC), suggest that droplet sizes range over four orders of magnitude (range: 0.6 to 1000 μm) and highly dependent on the type of expiratory event (Aliabadi et al., 2011; Gralton et al., 2011; Mittal et al., 2020). For example, Gralton et al. (2011) reported that healthy individuals produced even smaller particles compared to infectious individuals (0.05 μm - 500 μm) during breathing, coughing, sneezing and talking. However, the mechanism producing these droplets, their physico-chemical characteristics and infectivity are highly variable and there is a lack of clarity on these issues (Mittal et al., 2020).

Yan et al. (2018) reported that viral RNA measured in fine-ambient aerosols was also positively associated with influenza cases. In addition, geometric mean RNA copy numbers in a 30-minute exhaled breath of a seasonal influenza were 3.8×10^4 in fine (≤5 μm fractions) and 1.2×10^4 for coarse (>5 μm) droplets (Yan et al., 2018). This suggests that fine particles were >3-times more infectious in the case of seasonal influenza. A comparison of viral load, distance travelled and #RNA copies ejected during exhaled breath of a seasonal influenza in 30 min is presented in Table 2. If we consider size of a larger droplet as 10 μm and that of smaller droplet as 1 μm, larger droplet would have a million of viruses of 100 nm sizes whereas smaller virus will have only 1000 viruses (Table 2). The infectivity of smaller droplet reduces further when the droplet is dried in the atmosphere in sunlight exposure. Moreover, the viability of SARS-CoV-2 might decrease due to association with PM and thus, may be less infectious. However, there are limited studies on the combined effect of higher copy numbers, higher infectivity, less viral load and longer residence time for smaller droplets and this should be discussed in the future.

Table 2
A comparison of viral load, distance travelled and #RNA copies ejected during exhaled breath of a seasonal influenza in 30 min (Yan et al., 2018).

	Larger droplet	Smaller droplet
Size (μm)	10	1
Distance travelled	<1 m	>2 m
Residence time (s)	300	30,000
Number of CoV-2/droplet	1,000,000	1000
No. of droplets	1	1000
#RNA copies/30 min	1.20×10^4	3.80×10^4

4. Interaction and fate of droplet/droplet nuclei in the atmosphere

It should be noted that high temperature and relative humidity (RH) can enhance decay of SARS-CoV-2 and the addition of simulated sunlight can further cause a rapid decay of the virus in the droplet. The impact of meteorological parameters on the SARS-CoV-2 has been evaluated by recent studies as summarized in Fig. 3.

The SARS CoV-1 lost its infectivity after heating at 56 °C for 15 min but it was stable for at least 2 days following dryness on plastic and the loss of the virus infectivity was similar in both solution and dried forms (Chan et al., 2011). This may imply that droplet nuclei containing SARS-CoV-2 may behave in a similar manner as a dried droplet when exposed to temperature and humidity changes (Pani et al., 2020). An earlier study by Darnell et al. (2004) showed that ultraviolet light and extreme pH help to inactivate SARS-CoV-1. Another study showed that the virus survived only for few hours after losing its moisture content (Rabenau et al., 2005; Sizun et al., 2000). More recently, decay rates of SARS-CoV-1 and SARS-CoV-2 were compared at a temperature of 21–23 °C and 65% RH, revealing that both viruses were still detectable after 3 h of aerosolization (van Doremalen et al., 2020). This study also estimated the median half-life of SARS-CoV-2 to be 1.09 h which is similar to that of SARS-CoV-1 (1.18 h). Fears et al. (2020) showed that the infectivity of aerosolized SARS-CoV-2 was retained for 16 h at room temperature making it as a more suitable virus for airborne transmission. Recently, Schuit et al. (2020) studied the stability of SARS-CoV-2 in aerosols generated from virus suspended in different liquid matrices. Morris et al. (2020) found that SARS-CoV-2 virus can survive better under low temperature and high relative humidity (RH) conditions; median estimated virus half-life was more than 24 h at 10 °C and 40% RH. Thus, there is a mixed research on the role of temperature and humidity on the stability, viability and decay of viral activity. Notably, none of these studies have very clearly demonstrated the threshold values of ambient temperature and RH above which the virus would have a decreased fatality rates in case of SARS-CoV-2.

The time of decay of viruses using a predictive model in aerosols under different environmental conditions (such as temperatures, RH and UV) suggests that droplet nuclei (i.e., airborne SARS-CoV-2) is rapidly inactivated by simulated sunlight. The decay time (i.e., half-life, $t_{1/2}$)

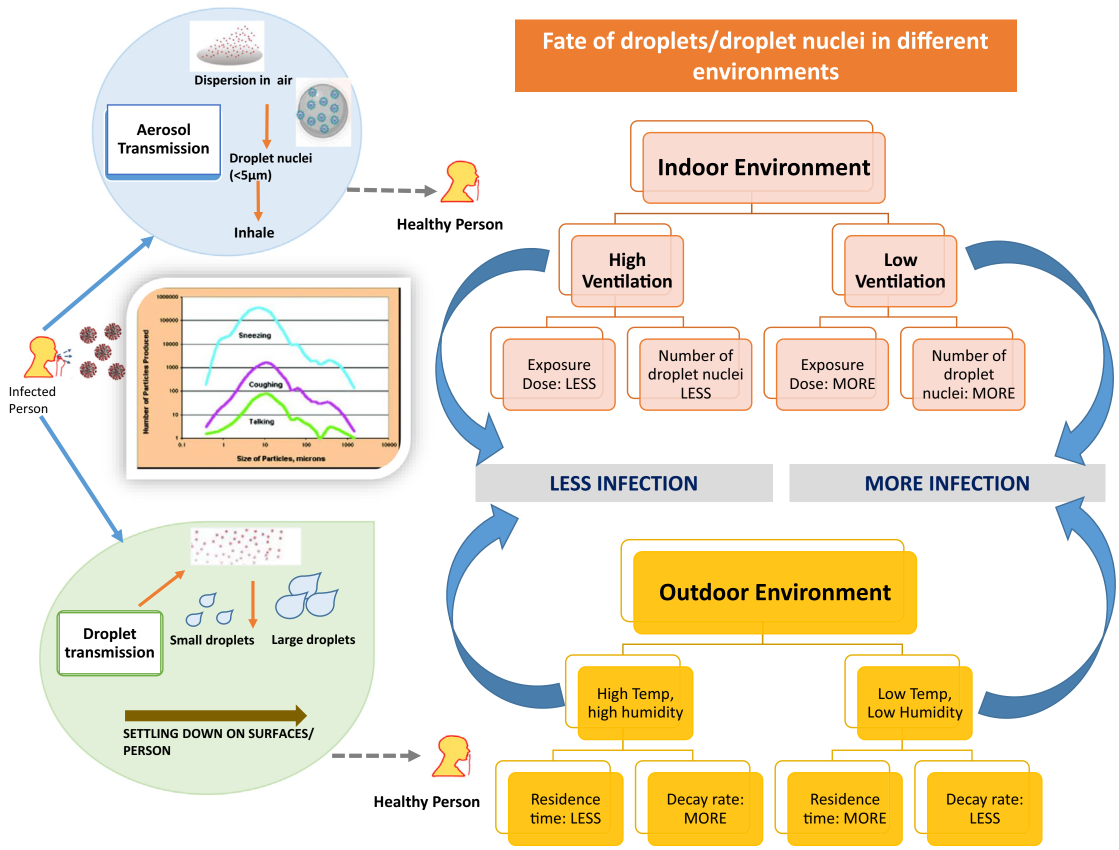

Fig. 3. Fate of droplet/droplet nuclei in different environment.

of SARS-CoV-2 on a surface can be calculated using the following equation.[7]

$$t_{1/2}\ (T, RH) = 32.43 - 0.62\ \mathrm{T} - 0.15\ \mathrm{RH}\ (\text{for } 74 \le T \le 95^\circ F \text{ and } 20 \le RH \le 60\%) \quad (1)$$

Earlier studies have shown that the transmission and outbreaks in case of influenza virus were dependent on the RH and T, especially in the temperate regions (Deyle et al., 2016; Lowen et al., 2007; Marr et al., 2019). These parameters are particularly important because once the virus gets associated or interacts with an atmospheric aerosol particle, the T and RH may govern the rate of denaturation of the protein and the evaporation of fine droplets (Vejerano and Marr, 2018). An increase in the temperature would increase the protein denaturation and hence, the infectivity power of the virus will decrease. Chan et al. (2011) studied the stability of SARS CoV-1 in 2003 outbreak and found that the virus infectivity didn't reduce significantly at high RH (>95%) at ambient temperature of 28 °C and 33 °C. In contrast, higher temperature (38 °C) but lower RH (80–90%) led to a loss of 0.25– 2 $\log_{10}$ titre in 24 h. Further, the authors found a higher reduction in viral titre in case of dried droplet and at higher RH (>95%) (Chan et al., 2011). In the light of above-mentioned studies, aerosol interaction and transmission in case of influenza virus can be a crucial to understand the COVID-19 spread.

5. Role of oxidizing radicals and UV radiation

Reactive oxygen and nitrogen metabolites play an important role in metabolic regulation and controlling spread of many diseases (Akaike, 2001; Peterhans, 1997; Pham-Huy et al., 2008; Yoo, 2018). Previous studies have emphasized that high ambient temperature and RH affect the lifecycle of viruses and reduce transmission, but the important underlying mechanisms remain unexplained. The most accepted mechanism of the virus fatality reduction inside human body or in the atmosphere, is the breaking of the peptide bond during reaction with oxidizing radicals (Yoo, 2018). Oxidizing radicals are highly reactive molecules with an unpaired electron. For example, nitric oxide (NO·—), superoxide anions (O_2·—), hydroxyl (OH·—) radicals and move drastically for pairing and are highly reactive. They can react with proteins by taking an electron and breaking the peptide bond, thereby deforming the structure of peptide bond. If this process occurs rapidly and at a larger scale, proteins or amino acids are destroyed and the fatality/infective power of the virus is reduced. A similar mechanism for destruction of nucleic acid by UV photolysis at 254 nm on viruses has been documented (Qiao et al., 2018; Walker and Ko, 2007; Ye et al., 2018). Therefore, under favourable meteorological conditions with higher solar UV radiation and RH, which enhance the production of several oxidizing species such as O_3 and OH radicals in the atmosphere, the SARS-CoV-2 virus adsorbed on ambient aerosol can become less infectious (Fig. 4).

Cutler and Zimmerman (2011) reviewed the possible mechanisms for inactivation of infectious agents via ultraviolet irradiation. Although, most of the UV-C radiation and partly UV-B are absorbed by O_3 in the stratosphere, these radiations on Earth surface can contribute to the inactivation of the SARS-CoV-2 causing an irreversible damage to DNA, unlike the bacteria. In fact, Yoo (2018) proposed that oxidizing radicals can attack the peptide bond even more effectively under high RH conditions compared to lower ambient temperature and RH due to accumulation of water on their surfaces, leading to a possible hydrogen bond formation with the droplet containing virus. Hence, ambient aerosols

[7] https://www.dhs.gov/science-and-technology/sars-calculator.

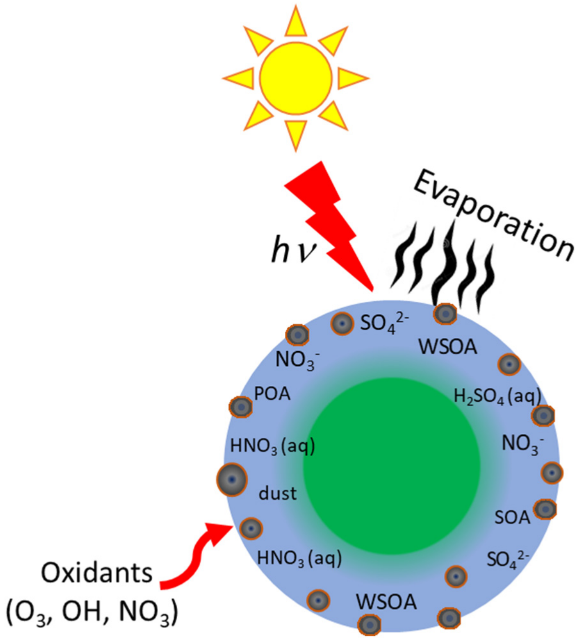

Fig. 4. Schematic diagram showing interaction of droplet nuclei containing SARS-CoV-2 with particulate matter, radiation and oxidants in the atmosphere. POA and WSOA are primary organic aerosol and water-soluble organic aerosols in the particulate matter.

may play an important role in airborne transmission of the virus, at least on a local scale and in indoor environment. However, an exact mechanism at molecular levels needs to be investigated to get a better understanding about the behaviour and infectivity of SARS-CoV-2, as well as the role of ambient aerosols in the transmission processes.

6. Issues on measurement of RNA activities, viability and decay

It is very important to note that the SARS-CoV-2 do not float freely in the air by themselves, rather they are contained within droplets or associated with atmospheric aerosols. These droplets are produced during exhalation of respiratory fluids and are composed of proteins, surfactants, salts, etc. (Vejerano and Marr, 2018). Apart from the physical parameters such as thermal heat and exposure to UV, the collision of a smaller droplet with atmospheric aerosol and/or adsorption on its surfaces, can denature the protein and reduce its infectivity. Therefore, such denatured smaller droplets would be less infectious than larger droplet.

Liu et al. (2020) found varying concentrations of SARS-CoV-2 RNA in ambient aerosol samples collected from different environments in Wuhan, where the measured RNA copies most likely got incorporated in ambient aerosol when particulate matter collided with the droplet nuclei containing SARS-CoV-2. However, it is not clear whether attachment of SARS-CoV-2 with PM will inhibit or intensify spread of the disease athough most of the studies point toward an intensification of COVID-19 in the presence of high levels of particulate matter over urban areas in the developed countries (Chen et al., 2020; Conticini et al., 2020; Contini and Costabile, 2020). More recently, RNA copies of the SARS-CoV-2 have been reported in fine-ambient aerosol samples (Chia et al., 2020), collected especially from/near hospital environments (Carducci et al., 2011). Belosi et al. (2021) reported concentrations of SARS-CoV-2 and probability of interactions with the pre-existing aerosol particles (i.e. PM) in outdoor air using a box model and found that the average outdoor concentration was <1 RNA copy m^{-3}.

These studies confirm the case for airborne transmission, indicating an association and/or adsorption of ejected droplet containing SARS-CoV-2 with ambient aerosols. However, in a few cases, the presence of SARS-CoV-2 virus has not been detected on surfaces and air vents, therefore, the probability of airborne transmission is expected to be quite low in the outdoor atmosphere (Chia et al., 2020; Dancer et al., 2020). Therefore, there is still no clear evidence on the susceptibility and viability of the SARS-CoV-2 virus in airborne transmission in the outdoor atmosphere (Pollitt et al., 2020) and the measured RNA copies could be simply from the sampling and measurement of ambient aerosols laden SARS-CoV-2. Furthermore, these studies have not performed any culture experiments (Liu et al., 2020), mainly due to inaccessibility to collect these droplet nuclei separately which makes it even more difficult to trace the source of SARS-CoV-2 RNA in ambient aerosols. However, in a recent study, Lednicky et al. (2020) measured SARS-CoV-2 RNA in ambient air of a clinic situated in a university student health care center and reported a concentration of 0.87 virus genomes L^{-1}. Thus, if the RNA is from dead virus, this would be non-infectious, inferring that infection and mortality would be simply due to virus-associated with ambient aerosols. Since the RNA quantification was done using a RT-PCR, it is unclear from this study if the measured RNA concentration was from a SARS-CoV-2 virus alone or SARS-CoV-2 mixed with ambient aerosols.

7. Lack of data on residence time (RT) of smaller droplets

The research, although limited, clearly indicate that the SARS-CoV-2 can survive in the atmosphere for considerable period of time either within the droplets/droplet nuclei or on the surface of an atmospheric aerosol. The residence time (RT) largely varies on different surfaces on/to which droplets are deposited/attached (Bhardwaj and Agrawal, 2020). In addition, the evaporation of ejected droplets can also affect its life-time (Biswas and Dhawan, 2020). The typical RT of PM is about a week, therefore, any association of the SARS-CoV-2 with ambient aerosols via adsorption on surfaces, especially $PM_{2.5}$, would allow the droplet nuclei to stay in the atmosphere as long as a week.

Most of the studies have suggested shorter RT for a droplet in the atmosphere and on different surfaces depending upon the size of the droplet or droplet nuclei (Setti et al., 2020b; Stadnytskyi et al., 2020; van Doremalen et al., 2020). For example, residence time of droplet nuclei of ~4 μm in diameter (equivalent to 12–21 μm droplets prior to dehydration), generated during normal speech, ranges from 8 to 14 min in a closed and stagnant environment (Stadnytskyi et al., 2020). Setti et al. (2020b) suggested that SARS-CoV-2 droplet nuclei of 1–3 μm diameter remain airborne and viable for up to 16 h (Fears et al., 2020). On the other hand, van Doremalen et al. (2020) performed an experiment with SARS-CoV-2 and SARS-CoV-1 viruses in five environmental conditions, and reported that SARS-CoV-2 remained viable in aerosols but infection probability is reduced significantly after 3 h. The different estimates of RT are likely due to different experimental/laboratory conditions such as ventilation which alters the T and RH of the environment (Fears et al., 2020; van Doremalen et al., 2020) and also possibly the use of different aerosolization media (Kormuth et al., 2018; Lin and Marr, 2020). Therefore, it is important to know the fate of the droplets after their ejection into the environment, i.e., RT, viral activity and the viability of virus in the atmosphere.

If the air containing SARS-CoV-2 is recirculated, which is very likely in an indoor setting, for example hospital rooms used for the treatment of COVID-19 patients or in restaurants, the entire room may be contaminated (Li et al., 2020). This study also reports that in the hospital indoor environment the viral RNA was mostly associated with atmospheric aerosols ≤2.5 μm (Liu et al., 2020). This is a very important finding because SARS-CoV-2 not only get associated with atmospheric aerosols, but also remain suspended in an indoor environment for several hours increasing their probability of getting recirculated without proper ventilation. Thus, it is imperative to study the fate of SARS-CoV-2 because if the contaminated air from the indoor hospital environment leaks out through the vents (Horve et al., 2020), the ambient atmosphere in the immediate vicinity of the vents would get further contaminated.

Therefore, re-circulating air with SARS-CoV-2 can contaminate the floors and walls, etc. (Li et al., 2020). Thus, estimating the RT of fine droplets in indoor environment with different ventilation and environmental settings becomes a crucial step in curbing the spread of COVID-19.

8. Conclusions and recommendations

The association of SARS-CoV-2 with ambient aerosols and its infective behaviour warrant a detailed investigation involving an interdisciplinary team because of the diverse experiments and their interpretations to get a complete understanding of the pandemic. We should study the fate and impact of these droplet nuclei in diverse indoor and outdoor environments. As suggested by many recent studies, a possible transmission of COVID-19 via ambient aerosols exists (Belosi et al., 2021) but a better understanding of association, interaction and transmission of the virus with ambient aerosols are the key to control its spreading for future prevention. This is particularly important as COVID-19 has still not subsided and there are second and third waves and even new strains of the same virus being reported in different parts of the world. In addition, there are a lot of factors affecting COVID-19 infection, such as underlying conditions involving immune system, behaviour, activity, and defense mechanism against infection of COVID-19 which play an important role to decide the fate of the virus within the human body.

Among several issues, the knowledge of exposure dose, exposure time of an individual to the virus and the residence time (RT) of the virus is very crucial. Earlier studies have provided an evidence for airborne transmission of measles virus (Remington et al., 1985) which was found to remain infectious in the air for up to 2 h in the infected environment. The longer a virus stays in the atmosphere, the extent of protein denaturation and probability of infection will increase. In contrast, the probability of a person getting infected may increase due to longer RT of the virus in the atmosphere. However, there is a lack of RT data of fine droplets in the atmosphere. Generally, RTs of fine droplets should be higher but the absence of any real data on RT measurement makes it more speculative. Moreover, the residence time of these droplets needs to be studied in different environmental conditions. Another important question that needs to be answered is threshold values of temperature and humidity at which the infectivity of SARS-CoV-2 will decrease/increase. In a recent study, Morris et al. (2020) found that survival of SARS-CoV-2 was relatively better at low temperatures and extreme relative humidity; median estimated virus half-life was more than 24 h at 10 °C and 40% RH. Although there are many studies which have attempted to define the impacts of temperature and RH on the infectivity of SARS-CoV-2, still there exists a huge ambiguity (Ahlawat et al., 2020).

Contini and Costabile (2020) argued whether high air pollution can influence COVID-19 outbreaks. Authors suggested that air pollutants, especially $PM_{2.5}$, may create inflammation and produce reactive oxygen species (ROS) through oxidation processes subsequently altering immunological processes as well. Although, this hypothesis may be true and exposure to high level of air pollution can weaken the human immune system, it's very difficult to conclude it to be a probable cause for death due to COVID-19. However, it is likely that it may act as a comorbid agent, which may worsen the recovery of COVID-19 patient. Contini and Costabile (2020) suggested that “the possibility of a detrimental effect of air pollution on the prognosis of patients affected by COVID-19 is plausible and deserves further investigation”. However, the association and role of air pollutants on COVID-19 spread is still illusive (Riccò et al., 2020) and should be investigated in future.

Bioavailability factor (AF_i) is a common term in pharmacology and refers to measurement of the rate and extent to which a drug reaches at the site of action. The estimation of exposure dose in airborne and droplet transmission is highly dependent on the bioavailability factor of the droplet and droplet nuclei, respectively. In case of airborne transmission, bioavailability factor is expected to be low compared to that for droplet transmission. Furthermore, AF_i is highly dependent on the natural-decay of SARS-CoV-2 as well as reduction in the viability due to evaporation of the droplet nuclei, interaction with contaminated surfaces of PM and other parameters such as temperature, UV and RH. Although there is no direct measurement of bioavailability factor for SARS-CoV-2, considering longer RT of droplet nuclei and previously mentioned factors, exposure dose would be fairly low for airborne transmission. Most importantly, all these investigations call for an urgent need to clearly define and to understand the airborne transmission. These are probable reasons why airborne transmission has not been very conclusive and accordingly a full understanding of the virus transmission is not achieved, thus restricting us to invent more effective preventive measures.

In summary, we believe that evaluating the association, interaction and transmission of SARS-CoV-2 virus with ambient aerosols is a key to understand its spread, carefully considering the recent experimental and field studies on the SARS-CoV-2 (Belosi et al., 2021). In particular, the interaction of SARS-CoV-2 with a certain type of atmospheric aerosols having a specific chemical composition is very important (Contini and Costabile, 2020). It is imperative to understand their behaviour if they are associated with fine black and organic carbon aerosols. However, the hypothesis still requires more studies and tests in both indoor and outdoor environments. Moreover, SARS-CoV-2 has been identified in the feces (Fei et al., 2020; Peccia et al., 2020) and the wastewater (Hata and Honda, 2020; Kumar et al., 2021; Kumar et al., 2020; Wurtzer et al., 2020). The research community needs to further study the fate of atmospheric aerosols associated with deadly SARS-CoV-2 by establishing an interdisciplinary team comprising of molecular biologists, virologists, physicists, chemists, mathematicians and modelers. This team should not only attempt to characterize the SARS-CoV-2 virus but also should aim to develop understanding on the fate of this virus in the environment by providing better estimations of exposure dose to minimize the spread of the disease.

CRediT authorship contribution statement

KR conceptualized the idea, completed reviews and wrote papers. All co-authors provided their inputs, edited and contributed to improve the paper by providing their suggestion/comments.

Declaration of competing interest

The authors declare no competing financial interest.

Acknowledgment

We would like to thank Kim Prather, Linsey Maar, Faye McNeill, Krystal J. Godri Pollitt, Akhilesh Kumar, Rakesh Singh, Prabir Patra and Heiko Oltmanns for fruitful discussion, Hrithivk Rajbhar for helping in drawing the figure, Arun Awasthi, Ayush Lepcha, Shashank Tripathi & Gyana Ranjan Tripathy for helpful edits. Although there was no grant provided for this project, the idea drawn is from KR's ongoing projects, Science and Engineering Research Board (SERB), Govt of India (Grant number: ECR#000490) and Department of Science and Technology, Ministry of Science and Technology, India (Grant number: DST/CCP/Aerosol/87/2017). We thank the two anonymous reviewers for their excellent comments/suggestion which helped improve this paper significantly.

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